CLEAR Outcomes Trial Review: Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

In February of 2020, the FDA approved bempedoic acid, sold under the brand name Nexletol, indicated for the treatment of heterozygous familial hypercholesterolemia (HeFH) as well as for patients with established atherosclerotic cardiovascular disease (ASCVD) who require additional low-density lipoprotein cholesterol (LDL-C) lowering. Initiated in 2016, the CLEAR Outcomes trial sought to assess the benefit of bempedoic acid monotherapy on cardiovascular (CV) outcomes. Results from the CLEAR Outcomes trial were published in December 2022 and demonstrated a lower risk of major adverse CV events (MACE; see description under Primary Endpoints in Table 1) in those who were treated with bempedoic acid compared with placebo.

Bempedoic acid is an ATP citrate lyase inhibitor. ATP citrate lyase is an enzyme that is found upstream of HMG-CoA reductase and causes up-regulation and increased clearance of LDL-C. Bempedoic acid is a prodrug activated by very-long chain acyl-coA synthetase-1, found in liver cells. Due to the fact that bempedoic acid does not have any activity within muscle cells, it is considered to be an appropriate alternative in patients who have demonstrated statin intolerance due to myalgia or myopathies.

Of note, **statin therapy continues to be the gold standard of treatment for LDL-C lowering**; patients should continue to be trialed on a maximally tolerated statin **before** non-statin alternatives are considered. Statin intolerance is defined as inability to tolerate ≥2 statins, with one trial of a low intensity statin. Refer to GLIN's February 2022 Lipid Guideline Update for a brief review of statin intensity and clinical indications according to the 2019 AHA/ACC Guidelines. Notably, the 2022 ACC ECDP on the Role of Nonstatin Therapies for LDL-Cholesterol which was published prior to the completion of the CLEAR Outcomes Trial, and therefore the treatment guideline at present do not reflect data discovered during this outcome trial as it relates to bempedoic acid.

As it relates to GLIN payer quality contracts, prescribing bempedoic acid for statin-intolerant patients with DM or CVD will NOT satisfy the statin use measures. **If a patient is *truly* statin-intolerant, they need to continue to be coded for statin intolerance annually** to remove them from statin metrics each measurement year. A review of statin exclusion codes can be found in GLIN's "Statin Rechallenge and Exclusion Reference".

Table 1. CLEAR Outcomes Trial Summary	
Study Design	Randomized, double-blind, placebo-controlled study conducted in 13,970 participants • Patients were randomized in a 1:1 fashion to treatment group or placebo • Median duration of follow-up: 40.6 months • Mean patient age: 65.5 years • Percent female: 48% • Percent with diabetes: 46%
Primary Endpoints	Experiencing at least one of the following major adverse CV events (MACE): • CV death • Nonfatal myocardial infarction (MI) • Nonfatal stroke • Coronary revascularization
Intervention	Bempedoic acid 180mg tablet by mouth once daily compared with a matching placebo tablet
Inclusion Criteria	• Men and nonpregnant, nonlacting women between 18 and 85 years of age • History of CVD (baseline incidence 14.8%), or at high risk for CVD including coronary artery disease (CAD; baseline incidence 51%), symptomatic peripheral arterial disease (PAD; baseline incidence 11.5%), cerebrovascular atherosclerotic disease, or at high risk for a cardiovascular (CV) event (baseline incidence 14.8%) • Patient-reported history of statin intolerance (defined in paragraph 3) • Patients who were receiving a very low average daily statin dose without unacceptable adverse effects could be enrolled (baseline statin use 23%) • Other lipid-lowering therapies were permitted, such as ezetimibe (baseline use 11.5%), niacin, bile acid resins, fibrates, or PCSK9 inhibitors, administered as monotherapy or in combination. • Fasting blood LDL-C ≥100 mg/dL (2.6 mmol/L) at screening; baseline characteristics: LDL-C 139 mg/dL; HDL-C 49 mg/dL; hsCRP 2.3 mg/L
Exclusion Criteria	• Fasting blood triglycerides >500 mg/dL (5.6 mmol/L) at screening • History of MACE within 90 days of screening, transient ischemic attack (TIA), or unstable or symptomatic cardiac arrhythmia • History of severe heart failure • Uncontrolled hypertension or uncontrolled diabetes
LDL-C Reduction	After 6 months of intervention, the bempedoic acid group demonstrated a **LDL-C lowering of 21.1%** (change in LDL-C at 6 months: -21.1 vs. -0.8 mg/dL [p < 0.06])
Incidence of a Primary Endpoint	**The incidence of MACE was 11.7% vs. 13.3%** (819 vs 927 patients, respectively); hazard ratio, 0.87; 95% confidence interval, 0.79 to 0.96; P=0.004 favoring bempedoic acid

Table 1. CLEAR Outcomes Trial Summary (continued)	

Secondary Outcomes	• Three-component MACE (nonfatal MI, nonfatal stroke, CV death): 8.2% vs. 9.5% (p = 0.006) favoring bempedoic acid
	  • Fatal or nonfatal MI: 3.7% vs. 4.8% (p = 0.002)
	  • Coronary revascularization: 6.2% vs. 7.6% (p = 0.001)
	  • Fatal or nonfatal stroke: 1.9% vs. 2.3% (p = 0.16)
	  • All-cause mortality: 6.2% vs. 6.0%
	• Change in hsCRP from baseline at 12 months: -20.6% vs. 0% (p < 0.05)
	• Any muscle disorder: 15.0% vs. 15.4%

Safety and Adverse Effects	Incidences of hyperuricemia, gout, and cholelithiasis were higher with bempedoic acid compared with placebo. • Hyperuricemia: 10.9% vs. 5.6% • Gout: 3.1% vs. 2.1% • Cholelithiasis: 2.2% vs. 1.2%

References:

1. FDA approves Bempedoic acid for treatment of adults with HeFH or established ASCVD. American College of Cardiology. https://www.acc.org/latest-in-cardiology/articles/2020/02/24/10/09/fda-approves-bempedoic-acid-for-treatment-of-adults-with-hefh-or-established-ascvd#:~:text=The%20U.S.%20Food%20and%20Drug,additional%20 lowering%20of%20LDL%2DC. Published February 24, 2020. Accessed March 15, 2023.

2. Bempedoic acid and cardiovascular outcomes in statin-intolerant ... The New England Journal of Medicine. https://www.nejm.org/doi/full/10.1056/NEJMoa2215024. Published March 4, 2023. Accessed March 15, 2023.

3. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. American College of Cardiology. https://www.jacc.org/doi/10.1016/j.jacc.2019.03.010. Published September 10, 2019. Accessed March 30, 2023.